include with this reply a fee authorization for the fee specified in 37 C.F.R. §1.17(p) to obtain consideration of the newly-cited references under 37 C.F.R. §1.97(c).

Remarks

Rejections over Havelund, *et al.*

The Examiner maintained rejection of Claims 1-3 under 35 U.S.C. §102(a) in light of Havelund, *et al.* (WO 95/07931), and of Claims 1-12, 25, and 26 under 35 U.S.C. §103 in light of Havelund, *et al.* (WO 95/07931) and two other references. In maintaining the rejection on these grounds, the Examiner alleged that the declaration executed by inventor Michael J. Beckage, which Applicants had previously submitted under 37 C.F.R. §1.131, was defective for not having been signed by both inventors. The Examiner indicated that submission of a declaration signed by both inventors would overcome the instant rejections.

Applicants submit a new declaration under 37 C.F.R. §1.131, executed by both inventors in order to traverse rejections founded on Havelund, *et al.* Applicants contend that the new declaration submitted with this response is properly executed by both inventors, and, together with copies of Michael J. Beckage's notebook pages (Exhibits 1, 2, and 3), establishes reduction to practice of the present invention before effective date of the Havelund, *et al.* reference. Applicants do not submit new copies of Exhibits 1, 2, and 3 with this response because, during the Office interview on December 17, 1997, the Examiner said that she could rely on the previously submitted Exhibits, which are already in the file.

As attested in the new declaration, and as recorded in the original signed and witnessed notebook pages of inventor Beckage, an aqueous solution of a fatty acid-acylated

insulin, namely, Nε-LysB29-palmitoyl-human insulin, referred to throughout the Exhibits as "C16-insulin" or simply as "C16" containing 0.35 mole of zinc per mole of fatty acid-acylated insulin (Exhibit 2), having 2.5 mg/mL of m-cresol (Exhibit 1) and a pH of approximately 7.5 (Exhibit 3), was prepared prior to 23 March, 1995, the effective 102(a) date of Havelund, *et al*. This composition meets all of the essential limits of Claim 1 and thus constitutes a reduction to practice of the invention defined by Claim 1 as of a date prior to 23 March 1995. Therefore, Applicants submit that Claims 1-3 are not rendered unpatentable by Havelund, *et al*. under 35 U.S.C. §102(a), nor are Claims 1-12, 25, and 26 rendered unpatentable by Havelund, *et al*. in light of other references under 35 U.S.C. §103. Applicants respectfully request the Examiner to withdraw the rejections founded on Havelund, *et al*.

Rejection under 35 U.S.C. §103

The Examiner rejected Claims 1-12, 25, and 26 under 35 U.S.C. §103(a) are allegedly unpatentable because of Muranishi in view of Hashimoto and Howey. Applicants respectfully traverse this rejection on the grounds that the cited references do not constitute a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, the Examiner must show:

1) some suggestion or motivation to modify or combine information in the prior art or pool of knowledge available to one of ordinary skill art at the time of filing the application;
2) a reasonable expectation of success in modifying or combining the prior art teachings, and
3) that the prior art references relied upon teach or suggest all the claim limitations.

Applicants contend that the cited references do not provide suggestion or motivation to combine their teachings,

nor do they provide a reasonable expectation of success because the Howey reference is inappropriate to the present invention.

Applicants suggest that the Examiner applied the Howey reference in the mistaken notion that formulations comprising fatty acid-acylated insulin analogs are within the scope of the pending claims. In support of this suggestion are the following passages from page 4 of the Office Action: "It would have been obvious . . . to palmitoylate the LysB28 position of the LysB28ProB29-human insulin of Howey et al." and "[m]otivation to produce palmitoyl LysB28ProB29-human insulin is provided by the expectation that the time profile of absorption of this derivative would be altered . . . ." The Examiner then cited both Howey and "the art" for providing motivation to add zinc to an insulin analog. In both quoted passages, it is obvious that the Examiner's premise is that formulations of palmitoylated LysB28ProB29-human insulin (a fatty acid-acylated insulin analog) are within the pending claims.

Applicants respectfully point out that claims to formulations of fatty acid-acylated insulin analogs were previously canceled. The present invention and claims do not involve acylated insulin analogs. Applicants assert that the rejection of the pending claims over art that may be relevant to formulations of acylated insulin analogs is not appropriate. Furthermore, Howey deals with insulin analogs that have quick onset and short duration of action, whereas, the subject matter of the pending claims deals with acylated insulin that have a delayed onset and a very protracted duration of action. Therefore, Applicants assert that Howey provides neither motivation or reasonable expectation of success in combining zinc with fatty acid-acylated insulin. In summary, Applicants contend that the Examiner has not made

a *prima facie* case of obviousness because of the inapplicability of the Howey reference in respect of the pending claims.

Summary

Applicants submit a declaration under 37 U.S.C. §1.131 executed by both Applicants to prove reduction to practice at a date prior to the Havelund publication. Applicants argue that the Examiner has failed to make a *prima facie* of obviousness against the claims that are now pending because the Howey publication provides insufficient motivation or expectation of success. Applicants respectfully request the Examiner to apply more relevant publications, or to remove the rejection of Claims 1-12, 25, and 26.

Respectfully submitted,

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